CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CLETHODIM

Chemical Code # 3566, Tolerance # 51917
SB 950 # New A.I.

11/9/93

I. DATA GAP STATUS

Combined, rat:	No data gap; no adverse effect
Chronic toxicity, dog:	No data gap; no adverse effect
Oncogenicity, rat:	See Combined, rat
Oncogenicity, mouse:	No data gap; no adverse effect
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; **possible adverse effect**
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required for this compound at this time.

Toxicology one-liners are attached.
All record numbers through #123832 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T931109

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 045; 115139; "Combined Chronic Oral/Oncogenicity Study in Rats with RE-45601 Technical (SX-1688)" (Author: Dougherty, K.K., Chevron Environmental Health Center, Richmond, CA, Lab. Project ID # SOCAL 2500, 11/1/88); 835; RE-45601 Technical (Batch/Lot # SX-1688, 83% purity) administered in diets containing 0, 0.15, 0.57, 16 and 86 mg a.i./kg/day to males and 0, 0.20, 0.72, 21, and 113 mg a.i./kg/day to females for two years; interim sacrifice of 10 rats/sex/dose at one year; incidence of mortality not significantly different from controls for any of the treated groups; most of the deaths occurred during the last quarter of the study; body weights of males and females treated at the highest dose were reduced during most of the study; decreased food consumption observed for this group of animals during the first year of the study; increased relative liver weights with trace to mild centrilobular hypertrophy were detected in both sexes treated at the highest dose at the end of the first year; at the end of the second year relative liver weight was increased in females at this dose level**; no adverse effects**; NOEL (M) = 16 mg/kg/day, (F) = 21 mg/kg/day (based on body weight reduction and liver weight changes with centrilobular hypertrophy); **acceptable**; (Leung, 9/7/93)

CHRONIC TOXICITY, DOG

** 035; 115064; "One-Year Oral toxicity Study in Dogs with Chevron RE-45601 Technical (SX-1688)" (author: Cox, R.H., Hazleton Laboratories America, Inc., Vienna, VA, Lab. Project ID # 2107-153, 10/28/88); 831; RE-45601 Technical (SX-1688, 83.3% purity) administered daily in gelatin capsules for 1 year to 6 beagle dogs/sex/dose; 0, 1, 75, or 200/300 mg/kg/day; high dose animals receiving 200 mg/kg/day during weeks 1-7 was increased to 300 mg/kg/day after day 31; all animals survived the study; **no adverse effects**; increased relative liver weights were reported in mid (116% - 125% of control, $p < 0.05$) and high (160% - 175% of control, $p < 0.05$) dose animals; elevated alanine aminotransferase and alkaline phosphatase as well as hepatocellular enlargement were detected in animals from the high dose groups; NOEL (M/F) = 1 mg/kg/day (based on increased relative liver weights and elevated liver enzyme levels); **acceptable**; (Leung, 8/30/93).

ONCOGENICITY, RAT

See Combined, rat

ONCOGENICITY, MOUSE

** 036; 115061; "Chronic Oral Oncogenicity Study in Mice with Chevron RE-45601 Technical (SX-1688)" (author: Cox, R.H., Hazleton Laboratories America, Inc., Vienna, VA, Lab. project ID #

2107-145, 10/25/88); 832; RE-45601 Technical (SX-1688, 83.3% purity) administered in diet to 60 mice/sex/dose; 0, 20, 200, 1000, or 2000 ppm; highest dose increased to 3000 ppm after 15th week; interim sacrifice of 10 mice/sex/dose after 52 weeks; lower survival for males and females in the 3000 ppm group through the 78th week; histopathlogical exams of tissues from unscheduled deaths revealed an increased incidence of systemic amyloidosis as a cause of death in the 3000 ppm group; mean relative liver weights were increased for the 1000 and 3000 ppm animals after 52 weeks of treatment and for 3000 ppm females after 78 weeks; microscopic findings indicated hepatic centrilobular hypertrophy and bile duct hyperplasia at the two highest doses at termination; increased incidence of lung adenomas and carcinoma in control and treated animals is not treatment-related due to the absence of a dose-response, a similar incidence in historical data, and late onset of the tumor (after week 52); **no adverse effects**; NOEL (M/F) = 200 ppm (based on liver weight changes and histological findings in the liver); **acceptable**; (Leung, 9/2/93).

REPRODUCTION, RAT

** 044; 115072; "Two Generation (One Litter) reproduction Study in Rats with RE-45601 Technical" (author: Tellone, C.I., Chevron Environmental Health Center, Inc., Richmond, CA, Lab. Project ID # CEHC 2596, 8/27/87); 834; RE-45601 Technical (SX-1688, 83.3% purity) administered in diet to 30 rats/sex/generation at nominal doses of 0, 5, 20, 500, and 2500 ppm for 2 generations; No test material-related changes in clinical observations or mortality were observed in either generation; mean body weights for both F_0 and F_{1a} adult males (88.0 to 93.5% control, $p<0.05$) and F_{1a} females (89.5% of control, $p<0.05$) were significantly reduced at 2500 ppm ith sporadic changes in food consumption; no treatment-related changes in reproductive parameters, necropsy and histopathology; **no adverse effects**; parental NOEL (M/F) = 500 ppm (decreased body weight), reproductive NOEL $\geq$ 2500 ppm (no effect at HDT); **acceptable**; (Leung, 10/12/93).

043; 115071; "Final Report: Pilot Rat Reproduction Study with Chevron RE-45601 Technical" (author: MacKenzie, K.M., Hazleton Laboratories America, Inc., Madison, WI, lab. Project ID # 6183-102, 5/12/86); RE-45601 Technical (SX-1688, 83.3% purity) administered in diet to 8 rats/sex/dose at 0, 500, 2000, or 5000 ppm for 1 week before mating; females and pups sacrificed on day 7 of lactation; all animals survived the study; reduced body weights in adults at the high dose level and in combined pup weights and weight gains at day 7 for all dose levels; no effect on reproductive parameters; **no adverse effects indicated**; paternal NOEL = maternal NOEL = 2000 ppm (based on body weight changes), developmental NOEL = 2000 ppm (based on pup weight changes); **supplemental**; (Leung, 10/7/93).

TERATOLOGY, RAT

** 040; 115068; "Teratology Study in Rats with Chevron RE-45601 Technical - Final Report" (author: Schroeder, R., Bio/Dynamics, Inc., East Millstone, NJ, Lab. Project ID # 86-3042, 7/20/87); 833; RE-45601 Technical (SX-1688, 83.3% purity) suspended in 0.7% carboxymethyl cellulose (w/v) and 0.5% tween 80 (w/v), were administered once daily to 25 pregnant CD rats/dose during days 6 - 15

of gestation; 0, 10, 100, 350, and 700 mg/kg/day; 5 dams from the 700 mg/kg/day group had died during day 11 - 16 of gestation; treatment at the two highest dose levels resulted in reduced maternal body weight and daily food consumption (days 6 - 10); clinical signs included excessive salivation and staining of skin/fur in the ano-genital area; fetal examinations revealed tail defects (absence of tail, short tail or filamentous tail) and retardation in ossification; **no adverse effects**; maternal NOEL = 100 mg/kg/day (based on reduced body weight, food consumption and clinical signs), developmental NOEL = 100 mg/kg/day (based on tail defects and retardation of ossification); **acceptable;** (Leung, 9/28/93).

038; 115066; "Pilot Teratology Study in Rats with Chevron RE-45601 Technical-Final Report" (Author:Schroeder, R. E., Bio/dynamics, Inc., East Millstone, NJ, Lab. Project ID # S-2807, 9/8/86); RE-45601 Technical (SX-1688, 83.3% purity) suspended in carboxymethyl cellulose/Tween 80 were given by gastric intubation to 10 pregnant CD rats/dose during days 6-15 of gestation; 0, 50, 150, 300 and 500 mg/kg/day; no adverse effects; all animals survived the study; excess salivation were noted in 4 females at the 300 mg/kg/day and 8 females at the 500 mg/kg/day dose levels; at 500 mg/kg/day, mean maternal weight gain between days 15-20 of gestation was reduced (61.2% of control, $p<0.05$); male fetal weight at the 500 mg/kg/day dose level was significantly reduced (88.8% of control, $p<0.01$); maternal NOEL = 150 mg/kg/day (based on body weight changes and salivation); developmental NOEL = 300 mg/kg/day (based on reduced mean fetal weight); **supplemental**; (Leung, 9/23/93).

TERATOLOGY, RABBIT

** 039; 115067; "Teratology Study in Rabbits with Chevron RE-45601" (author: Dearlove, G.E., Argus Research Laboratories, Inc., Horsham, PA, Lab. Project ID # 303-007, 1/30/87); RE-45601 Technical (SX -1688, 83.3% purity) suspended in 0.7% carboxymethyl cellulose (w/v) and 0.5% tween 80 (w/v), were administered once daily to 20 artificially inseminated Hra:(NZW)SPF rabbits/dose on days 7 through 19 of gestation; 0, 25, 100, or 300 mg/kg/day; one mid dose rabbit had died on day 17; necropsy of this doe revealed gastric ulceration and red fluid-like substance present in the uterus suggesting an impending abortion; one low dose rabbit aborted all five of its conceptuses on day 22; decreased maternal body weight gain reported in mid and high dose animals with reduced food consumption in only high dose rabbits; reproductive parameters were not affected by treatment; **no adverse effects**; maternal NOEL = 25 mg/kg/day (reduced body weight gain and food consumption), Developmental NOEL $\geq$ 300 mg/kg/day (no effect at HDT); **acceptable**; (Leung, 9/24/93).

037; 115065; "Pilot Teratology Study in Rabbits with Chevron RE-45601 Technical" (Author: Dearlove, G.E., Argus Research Laboratories, Inc., Horsham, PA, Lab. Project ID # 303-007P, 7/15/86); RE-45601 technical (SX-1688, 83.3% purity) suspended in aqueous 0.7% carboxymethyl cellulose (w/v) and 0.5% Tween 80 (w/v) was given by gastric intubation to 8 artificially inseminated Hra:(NZW)SPF rabbits/dose on days 7 through 19 of gestation; 0, 50, 150, 300, or 500 mg/kg/day; **possible adverse effects indicated**: 300 and 500 mg/kg/day dosages were maternally toxic as indicated by significantly higher incidences of gastrointestinal lesions (hairball and/or ulceration) and reduced maternal body weights with decreased food consumption; abortions and premature deliveries were also increased for high dose pregnant rabbits; maternal NOEL = 150 mg/kg/day (based on GI lesions, abortions and premature

deliveries), developmental NOEL = 500 mg/kg/day (no significant effects at HDT); **supplemental**; (Leung, 9/22/93).

GENE MUTATION

** 046; 115140; "Microsomal/Mammalian Microsome Mutagenicity Plate Incorporation Assay with RE-45601 (83% purity, SX-1688) and with RE-45601 Technical (83.3% purity, SX-1688)" (author: Machado, M.L., Chevron Environmental Health Center, Inc., Richmond, CA, Lab. Project ID #s Socal 2505, CEHC 2555, 1/13/86, 4/28/86); 842; RE-45601 (SX-1688, 83 - 83.3% purity); tested with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and E. Coli WP2 uvrA at dose levels of 0 (DMSO) and 0.1 to 10 mg/plate with and without activation by Aroclor-induced rat liver S9 fraction; 48 hour incubation; triplicate plates; 2-3 trials; **no adverse effect**; positive controls functional; no reproducible increases in mutant frequency; **acceptable**; (Leung, 10/13/93)

CHROMOSOME EFFECTS

047; 115141; "Cytogenetics Assay in Bone Marrow Cells of Rats Following Acute Oral Exposure to RE-45601 Technical" (author: Putman, D.L., Microbiological Associates, Inc., Bethesda, MD, Lab. Project ID # T5072.105, 2/11/87); 843; RE-45601 Technical (SX-1688, 83.3% purity) suspended in 0.7% CMC/1% Tween 80; single doses of 0, 0.15, 0.50, or 1.5 g/kg was administered orally by gavage to 5 Sprague Dawley rats/sex/dose; 2 to 4 hours prior to sacrifice at 12, 24, and 48 hours, rats were treated with colchicine (1 mg/kg, ip); 50 metaphase cells/animal were examined; **no adverse effects; positive controls functional; RE-45601 Technical did not induce chromosomal aberrations in the bone marrow cells of male or female rats; **acceptable**; (Leung, 10/15/93)

050; 115144; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells with Chevron RE-45601 Technical" (author: Putman, D.L., Microbiological Associates, Inc., Bethesda, MD, Lab. Project ID # T4529.337, 7/22/86); RE-45601 Technical (SX-1688, 81.4% purity); tested in Chinese Hamster Ovary Cells with and without activation by Aroclor 1254 induced rat liver S9 fraction; duplicate flasks/dose/trial; 2 trials; 100 cells scored/dose; 0 (DMSO), and a dose range of 0.03 to 1.2 ul/ml; 2- and 8- hour exposure with and without S9 activation, respectively; **possible adverse effect: significant increase in the frequency of structural aberrations/cell at 1 ul/ml in the absence of S9 activation; no increase in structural aberrations were reported in the activated system; similar results were observed in a confirmatory assay; **acceptable**; (Leung, 10/18/93).

051; 115145; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells with Purified Chevron RE-45601" (author: Putman, D.L., Microbiological Associates, Inc., Bethesda, MD, Lab. Project ID # S-2865, 12/15/86); RE-45601 (SX-1718, 96.1% purity); tested in Chinese Hamster Ovary Cells with and without activation by Aroclor 1254 induced rat liver S9 fraction; duplicate flasks/dose/trial; 2 trials; 100 cells scored/dose; 0 (DMSO), and a dose range of 0.03 to 1.2ul/ml; 2- and 8- hour exposure with and without S9 activation, respectively; **no adverse effect**; a small increase in aberrations/cell was reported at 0.1 ul/ml in the presence of S9 activation; however, this increase was not

confirmed in the second trial and was therefore not considered to be biologically significant; purified RE-45601 did not induce structural chromosomal aberrations; **supplemental**; (Leung, 10/18/93).

One chromosomal aberration study with the CHO cells had demonstrated an increased frequency of structural aberrations/cells in the absence of metabolic activation. However, this effect was not reproduced in the another separate study employing oral exposure and is therefore regarded as weak evidence for clastogenic activity.

DNA DAMAGE

054; 115148; "In Vivo-In Vitro Hepatocyte DNA Repair Assay: In Vitro Evaluation of Unscheduled DNA Synthesis (UDS) Following Oral Administration of Chevron RE-45601 Technical to $B_6C_3F_1$ " (authors: Steinmetz, K.L. and Mirsalis, J.C., SRI International, Menlo Park, CA, Lab. Project ID # LSC-1960, 8/7/86); RE-45601 Technical (SX-1688, 83.3% purity); tested in $B_6C_3F_1$ male mouse hepatocytes; 3-5 mice/dose; 0, 100, 1000, and 5000 mg/kg; mice sacrificed at 2 and 16 hours post-treatment; cells labelled in vitro 4 hours with 3H-Tdr and chased 14 to 18 hours with unlabeled thymidine; UDS by autoradiography; 30 cells scored on each of 3 slides for each mouse; **no adverse effects; positive control functional; RE-45601 Technical did not induce UDS following oral gavage at dose levels of 5000, 1000, and 100 mg/kg in male $B_6C_3F_1$ mice; **acceptable**; (Leung, 10/19/93).

NEUROTOXICITY

Not required for this compound at this time.

STUDIES ON METABOLITES

030; 115047; "Five-Week Oral Toxicity Study in Rats with RE-47719 (SX-1800)" (author: Bagos, A.C. and Beatty, P.W., Chevron Environmental Health Center, Inc., Richmond, CA, Lab. Project ID # CEHC 2949, 11/15/88); RE-47719 (Batch # SX-1800, 99.3% purity) administered in diet containing 0, 80.8, 871 or 7820 ppm for 5 weeks; 10 Sprague Dawley rats/sex/dose; no unscheduled deaths occurred; one low dose male was sacrificed because of injury-related clinical findings associated with a broken bridge of the nose; high dose males exhibited reduced body weight due to decreased food consumption; elevated mean absolute and relative liver weights in males (114 - 119% of control, $p < 0.01$) and females (115 - 117% of control, $p < 0.05$) at the high dose without any correlative histopathological changes reported; **no adverse effects indicated**; **supplemental**; (Leung, 7/29/93).

041; 115069; "Oral Teratogenicity and Developmental Toxicity Screen in Rats with Chevron RE-47719" (author: Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA, Lab. Project ID # 303-012, 11/8/88); 833; RE-47719 (clethodim imine sulfone, SX-1800, 98.6% purity) administered orally in aqueous 0.7% carboxymethyl cellulose and 1% Tween 80 to 10 pregnant CD rats/dose at 0, 10, 100, or 700 mg/kg/day on days 6 through 15 of gestation; all animals survived the

study; three high dose rats exhibited excess salivation occurring on a total of 5 days; reduced maternal weight gain with decreased daily food consumption was observed at 700 mg/kg/day; fetal body weights were significantly decreased for the high dosage group litters as compared to control group; increased fetal and litter incidences of cervical ribs at the high dose; analysis of fetal ossification site averages revealed a significant decrease in the average number of sternal ossification sites in the high dose group; **no adverse effects indicated**; maternal NOEL = 100 mg/kg/day (reduced body weight gain and food consumption), developmental NOEL = 100 mg/kg/day (retarded ossification); **supplemental**; (Leung, 10/1/93).

049; 115143; "Microbial/Mammalian Microsome Plate Incorporation Mutagenicity Assay with RE-47719 (SX-1800)" (author: Machado, M.L., Chevron Environmental Health, Inc., Richmond, CA, CEHC 2948, 10/19/88); 842; RE-47719 (SX-1800, 98.6% purity); tested with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and E. Coli WP2 uvrA at dose levels of 0 (DMSO) and 0.1 to 10 mg/plate with and without activation by Aroclor-induced rat liver S9 fraction; 48 hour incubation; triplicate plates; 2 trials; **no adverse effects indicated**; RE-47719 was not mutagenic with or without metabolic activation; **supplemental**; (Leung, 10/13/93)

052; 115146; "Chromosome Aberration in Chinese Hamster Ovary (CHO) Cells with RE-47719 Final Toxicology Report" (author: Putman, D.L., Microbiological Associates, Inc., Bethesda, MD, Lab. Project ID # T8226.337003 MRA, 11/3/88); RE-47719 (SX-1800, 99.3% purity); tested in Chinese Hamster Ovary Cells with and without activation by Aroclor 1254 induced rat liver S9 fraction; duplicate flasks/dose/trial; 1 trial; 100 cells scored/dose; 0 (acetone), 50, 100, 200, and 400 ug/ml; 2- and 10-hour exposure with and without S9 activation, respectively; **no adverse effect indicated**; RE-47719 was negative in the CHO cytogenetics assay; **supplemental**; (Leung, 10/19/93)

031; 115048; "Five-Week Oral Toxicity Study in Rats with RE-51228 (SX-1803)" (authors: Bagos, A.C. and Beatty, P.W., Chevron Environmental Health Center, Inc., Richmond, CA, Lab. Project # CEHC 2950, 11/15/88); RE-51228 (Lot/Batch # SX-1803, 94.8% purity) administered in diet daily for 5 weeks; average test material intake: M - 0, 5.94, 67.7, and 588 mg/kg/day, F - 0, 6.43, 75.5, and 663 mg/kg/day; 10 Sprague Dawley rats/sex/dose; clinical findings included open sores, scab, thinning of fur, malocclusion, and ocular or nasal discharge were observed in no more than three males and one female per dose group; no mortality or signs of toxicity were observed that could be attributed to the test material; no compound-related macroscopic or microscopic pathological changes were reported; NOEL (M) $\geq$ 588 mg/kg/day, (F) $\geq$ 663 mg/kg/day (based on no effects observed at HDT); **supplemental**; (Leung, 8/18/93).

042; 115070; "Oral Teratogenicity and Developmental Toxicity Screen in Rats with RE-51228" (author: Hoberman, A.M., Argus Research Laboratories, Inc., Horsham, PA, Lab. Project ID # 303-010, 11/8/88); 833; RE-51228 (5-OH clethodim sulfone, SX-1796, 99.9% purity) administered orally in aqueous 0.7% carboxymethyl cellulose and 1% Tween 80 to 10 pregnant CD rats/dose at 0, 10, 100, or 700 mg/kg/day on days 6 through 15 of gestation; all animals survived the study; two high dose rats exhibited rales and another rat had excess salivation; no adverse effects indicated: administration of

RE-51228 to dams as high as 700 mg/kg/day did not result in fetal malformations or variations; maternal NOEL = 100 mg/kg/day (clinical signs), developmental NOEL $\geq$ 700 mg/kg/day (no effect at HDT); **supplemental**; (Leung, 10/4/93).

048; 115142; "Microbial/Mammalian Microsomal Plate Incorporation Mutagenicity Assay with RE-51228" (author: Machado, M.L., Chevron Environmental Health, Inc., Richmond, CA, Lab. Project ID # CEHC 2856, 12/7/87); 842; RE-51228 (batch # and purity not provided); tested with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and E. Coli WP2 uvrA at dose levels of 0 (acetone) and 0.03 to 5 mg/plate with and without activation by Aroclor-induced rat liver S9 fraction; 48 hour incubation; triplicate plates; 2 trials; **no adverse effects indicated**; RE-51228 was not mutagenic with or without metabolic activation; **supplemental**; (Leung, 10/13/93)

053; 115147; "Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells: RE-51228" (author: Putman, D.L., Microbiological Associates, Inc., Bethesda, MD, Lab. Project ID # T8227.337003, 11/7/88); RE-51228 (SX-1796, 99.9% purity); tested in Chinese Hamster Ovary Cells with and without activation by Aroclor 1254 induced rat liver S9 fraction; duplicate flasks/dose/trial; 1 trial; 100 cells scored/dose; 0 (acetone), 313, 625, 1250, and 2500 ug/ml; 2- and 10- hour exposure with and without S9 activation, respectively; **no adverse effects indicated**; RE-51228 was negative in the CHO cytogenetics assay; **supplemental**; (Leung, 10/19/93)